FORM PTO-1390 (REV 5-93) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: von Kreisler.015

U.S. APPLICATION NO. (If known, see 37 CFR 1.5): 09/914015

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP00/01357	February 18, 2000	February 21, 1999

TITLE OF INVENTION: "PAINLESS AND TISSUE SAVING INJECTION OF MEDICAMENTS"

APPLICANT(S) FOR DO/EO/US: B. Braun Melsungen AG [DE/DE]

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US)
6. ☒ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☒ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.
8. ☒ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☐ Other items or information:

U.S. APPLICATION NO (If known, see 37 C.F.R. 1.5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
09/914015	PCT/EP00/01357	von Kreisler.015

17. [X] The following fees are submitted:	CALCULATIONS	PTO USE ONLY
Basic National Fee (37 CFR 1.492(a)(1)-(5)): Search Report has been prepared by the EPO or JPO.....	$860.00	
International preliminary examination fee paid to USPTO (37 CFR 1.482)		
No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2))..		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37CFR 1.445(a)(2)) paid to USPTO.....		
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4).....		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 860.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$	

Claims	Number Filed		Number Extra	Rate		
Total claims	82	-20 =	62	X 18.00	$ 1,116.00	
Independent Claims	8	-3 =	5	X 80.00	$ 400.00	
Multiple dependent claims(s) (if applicable)				+	$	
TOTAL OF ABOVE CALCULATIONS =					$ 2,376.00	
Reduction by 1/2 for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28).					$	-
SUBTOTAL =					$	
Processing fee of **$130.00** for furnishing the English translation later the [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				+	$	
TOTAL NATIONAL FEE =					$	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property				+	$	
TOTAL FEES ENCLOSED =					$ 2,376.00	
					Amount to be: refunded	$
					charged	$

a. [X] A check in the amount of $2,376.00 to cover the above fees is enclosed.

b. [ ] Please charge my Deposit Account No. _____ in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. [X] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 04-1406. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

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28,833
REGISTRATION NUMBER

PATENT
Attorney Docket von Kreisler.015

THE UNITED STATES PATENT AND TRADEMARK OFFICE

United States Serial No.	:	[To be assigned]
International Application No.	:	PCT/EP00/01357
International Filing Date	:	February 18, 2000
Applicant	:	B. BRAUN MELSUNGEN AG [DE/DE]
Inventors	:	Bernd H. Meier and Iris Jankowiak-Meier
Title	:	"PAINLESS AND TISSUE SAVING INJECTION OF MEDICAMENTS"

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BOX -- PCT
Commissioner for Patents
United States Patent and Trademark Office
Washington, D.C. 20231

PRELIMINARY AMENDMENT UNDER 37 C.F.R. § 1.111

Dear Sir:

The claims filed in International Patent Application PCT/EP00/01357 were amended on April 24, 2001. A copy of claims 1-77 as amended on April 24, 2001 is attached hereto as Exhibit A.

In the specification

Please insert at page 1, line 1 of the specification, the following:

-- This application is a national phase filing under 35 U.S.C. § 371 of International Application No. PCT/EP00/01357, filed February 18, 2000, which claims priority from German Application No. 199 07 257.4, filed February 21, 1999. --

In the claims:

Please cancel claims 1-27, 50, 53 and 77 without prejudice to reintroduction of such claims in the prosecution of this Application. Please add the following new claims 78-112.

78. The kit according to claim 28 wherein the components (a) and (b) are isolated in separate sealed containers.

79. The kit according to claim 48 wherein at least part of the cation and/or anion component(s) is replaced by a polyol.

80. A method of reducing local vascular damage of the perivascular connective tissue of a mammal during the administration of medicament into an injection vessel of said mammal, said method comprising the step of administering into the vessel a medicament comprising (a) colloid-forming macromolecules in an aqueous solution and (b) a pharmaceutically active ingredient.

81. The method of claim 80 wherein the mammal is a human being.

82. A method of reducing pain normally experienced by a human being during the administration of medicaments into an injection vessel of a human being, said method comprising the step of administering into the vessel medicament comprising (a) colloid-forming macromolecules in an aqueous solution and (b) a pharmaceutically active ingredient.

83. A method of reducing diffusion of pharmaceutically active ingredient through the walls of an injection vessel of a human being after administration of the ingredient into a vessel, said method comprising the step of administering into the vessel an aqueous solution comprising the active ingredient and colloid-forming macromolecules.

84. The method according to claim 81, characterized in that said macromolecule is selected from the group consisting of polysaccharides, modified polysaccharides, peptides, modified peptides, and albumins.

85. The method according to claim 84, characterized in that said polysaccharide is selected from the group consisting of cellulose, starch and dextrane.

86. The method according to claim 84, characterized in that said modified polysaccharide is hydroxyethylstarch [poly (O-hydroxyethyl) starch].

87. The method according to claim 86, characterized in that said hydroxyethylstarch has a degree of substitution, DS, of < 0.4 and an average molecular weight of below 300,000.

88. The method according to claim 82, characterized in that said macromolecule is selected from the group consisting of polysaccharides, modified polysaccharides, peptides, modified peptides, and albumins.

89. The method according to claim 88, characterized in that said polysaccharide is selected from the group consisting of cellulose, starch and dextrane.

90. The method according to claim 88, characterized in that said modified polysaccharide is hydroxyethylstarch [poly (O-hydroxyethyl) starch].

91. The method according to claim 88, characterized in that said hydroxyethylstarch has a degree of substitution, DS, of < 0.4 and an average molecular weight of below 300,000.

92. The method according to claim 83, characterized in that said macromolecule is selected from the group consisting of polysaccharides, modified polysaccharides, peptides, modified peptides, and albumins.

93. The method according to claim 92, characterized in that said polysaccharide is selected from the group consisting of cellulose, starch and dextrane.

94. The method according to claim 92, characterized in that said modified polysaccharide is hydroxyethylstarch [poly (O-hydroxyethyl) starch].

95. The method according to claim 94, characterized in that said hydroxyethylstarch has a degree of substitution, DS, of < 0.4 and an average molecular weight of below 300,000.

96. The method according to claim 84, characterized in that gelatin is employed as polypeptide.

97. The method according to claim 84, characterized in that the modified polypeptide is selected from the group consisting of oxypolygelatin or gelatin succinate.

98. The method according to claim 97, characterized in that said modified polypeptide has an average weight of below 400,000.

99. The method according to claim 97, characterized in that said modified polypeptide has an average molecular weight of below 15,000.

100. The method according to claim 96, characterized in that said albumins are selected from the group consisting of human albumin, cleavage products of albumin, and recombinant human serum albumin.

101. The method according to claim 81, characterized in that said colloid-forming macromolecules have a colloid-osmotic pressure in aqueous solution of > 1333 Pa (10 mm Hg).

102. The method according to claim 82, characterized in that said colloid-forming macromolecules have a colloid-osmotic pressure in aqueous solution of > 3733 Pa (28 mm Hg).

103. The method according to claim 83, characterized in that the proportion of the colloid-forming macromolecules is from 2 to 25% by weight, based on the total amount of the injectable aqueous solution.

104. The method according to claim 83, characterized in that the proportion of the colloid-forming macromolecules is from 3 to 5% by weight, based on the total amount of the injectable aqueous solution.

105. The method according to claim 83, characterized in that said injectable aqueous solution additionally has a cation proportion of from 100 to 170 mmol/l and an anion proportion of from 100 to 170 mmol/l.

106. The method according to claim 83, characterized in that said injectable aqueous solution additionally has a cation proportion of from 100 to 150 mmol/l and an anion proportion of from 100 to 150 mmol/l.

107. The method according to claim 106, characterized in that part of the cation and/or anion concentration is replaced by a sugar or a polyol.

108. The method according to claim 83, characterized in that said injectable aqueous solution has an osmolarity of between 250 and 400 mOsmol/l.

109. The method according to claim 83, characterized in that said pharmaceutically active ingredient is contained in a proportion of from 0.5 to 25% by weight, based on the total amount of the injectable aqueous solution.

110. The method according to claim 81, characterized in that said pharmaceutically active ingredient is selected from the group consisting of slimming preparations/anorexiants, acidose therapeutics, amino acids (*e.g.*, histidine) or modified amino acids, analeptics/antihypoxemics, analgetics/antirheumatics, anthelmintics, antiallergics, antianemics, antiarrhythmics, antibiotics/antiinfectives, antidementives (nootropics), antidiabetics, antidotes, antiemetics/antivertiginosics, antiepileptics, antihemorrhagics (antifibrinolytics and other

hemostatics), antihypertensives, antihypoglycemics, antihypotensies, anticoagulants, antimycotics, antiparasitics (internal), antiphlogistics, antitussives/expectorants, anti-arteriosclerosis agents, balneotherapeutics and agents for heat therapy, beta receptor and calcium channel blockers and inhibitors of the renin-angiotensin system, broncholytics/antiasthmatics, cholagogics and bile duct therapeutics, cholinergics, corticoids (internal), dermatics (internal), dietetics/nutrition therapeutics, diagnostics and agents for diagnostic preliminaries, diuretics, agents stimulating blood flow, withdrawal agents, enzyme inhibitors, enzyme preparations and transport proteins, fibrinolytics, geriatric agents, gout agents, influenza remedies, gynecologic agents, anti-hemorrhoidal agents (proctologics), hepatics, hypnotics/sedatives, hypophysis and hypothalamus hormones, regulatory peptides and their inhibitors, immunotherapeutics and cytokines, infusion and standard injection solutions, organ perfusion solutions, cardiacs, anti-caries and anti-parodontosis agents and other dental preparations, coronary agents, laxants, lipid depressants, neural therapeutics, gastro-intestinal agents, migraine remedies, mineral preparations, muscle relaxants, narcotics, parathyroid hormones/calcium-metabolic regulators/osteoporosis remedies, neuropathy preparations and other neurotropic agents, neurotransmitters (*e.g.*, dopamine) or modified neurotransmitters, ophthalmics, otologics, Parkinson remedies and other remedies against extrapyramidal disturbances, psychopharmacons, sinusitis remedies, roborants/tonics, thyroid therapeutics, serums, immunoglobulins and vaccines, sexual hormones and inhibitors, spasmolytics, platelet aggregation inhibitors, tuberculosis remedies, alterants, urologic agents, vein therapeutics, vitamins, wound treatment agents, cytostatics and metastasis inhibitors.

111. The method, according to claim 82, characterized in that said pharmaceutically active ingredient is selected from the group consisting of slimming preparations/anorexiants,

acidose therapeutics, amino acids (*e.g.*, histidine) or modified amino acids, analeptics/antihypoxemics, analgetics/antirheumatics, anthelmintics, antiallergics, antianemics, antiarrhythmics, antibiotics/antiinfectives, antidementives (nootropics), antidiabetics, antidotes, antiemetics/antivertiginosics, antiepileptics, antihemorrhagics (antifibrinolytics and other hemostatics), antihypertensives, antihypoglycemics, antihypotensies, anticoagulants, antimycotics, antiparasitics (internal), antiphlogistics, antitussives/expectorants, anti-arteriosclerosis agents, balneotherapeutics and agents for heat therapy, beta receptor and calcium channel blockers and inhibitors of the renin-angiotensin system, broncholytics/antiasthmatics, cholagogics and bile duct therapeutics, cholinergics, corticoids (internal), dermatics (internal), dietetics/nutrition therapeutics, diagnostics and agents for diagnostic preliminaries, diuretics, agents stimulating blood flow, withdrawal agents, enzyme inhibitors, enzyme preparations and transport proteins, fibrinolytics, geriatric agents, gout agents, influenza remedies, gynecologic agents, anti-hemorrhoidal agents (proctologics), hepatics, hypnotics/sedatives, hypophysis and hypothalamus hormones, regulatory peptides and their inhibitors, immunotherapeutics and cytokines, infusion and standard injection solutions, organ perfusion solutions, cardiacs, anti-caries and anti-parodontosis agents and other dental preparations, coronary agents, laxants, lipid depressants, neural therapeutics, gastro-intestinal agents, migraine remedies, mineral preparations, muscle relaxants, narcotics, parathyroid hormones/calcium-metabolic regulators/osteoporosis remedies, neuropathy preparations and other neurotropic agents, neurotransmitters (*e.g.*, dopamine) or modified neurotransmitters, ophthalmics, otologics, Parkinson remedies and other remedies against extrapyramidal disturbances, psychopharmacons, sinusitis remedies, roborants/tonics, thyroid therapeutics, serums, immunoglobulins and vaccines, sexual hormones and inhibitors, spasmolytics, platelet aggregation inhibitors, tuberculosis

remedies, alterants, urologic agents, vein therapeutics, vitamins, wound treatment agents, cytostatics and metastasis inhibitors.

112. The method according to claim 83, characterized in that said pharmaceutically active ingredient is selected from the group consisting of slimming preparations/anorexiants, acidose therapeutics, amino acids (*e.g.*, histidine) or modified amino acids, analeptics/antihypoxemics, analgetics/antirheumatics, anthelmintics, antiallergics, antianemics, antiarrhythmics, antibiotics/antiinfectives, antidementives (nootropics), antidiabetics, antidotes, antiemetics/antivertiginosics, antiepileptics, antihemorrhagics (antifibrinolytics and other hemostatics), antihypertensives, antihypoglycemics, antihypotensies, anticoagulants, antimycotics, antiparasitics (internal), antiphlogistics, antitussives/expectorants, anti-arteriosclerosis agents, balneotherapeutics and agents for heat therapy, beta receptor and calcium channel blockers and inhibitors of the renin-angiotensin system, broncholytics/antiasthmatics, cholagogics and bile duct therapeutics, cholinergics, corticoids (internal), dermatics (internal), dietetics/nutrition therapeutics, diagnostics and agents for diagnostic preliminaries, diuretics, agents stimulating blood flow, withdrawal agents, enzyme inhibitors, enzyme preparations and transport proteins, fibrinolytics, geriatric agents, gout agents, influenza remedies, gynecologic agents, anti-hemorrhoidal agents (proctologics), hepatics, hypnotics/sedatives, hypophysis and hypothalamus hormones, regulatory peptides and their inhibitors, immunotherapeutics and cytokines, infusion and standard injection solutions, organ perfusion solutions, cardiacs, anti-caries and anti-parodontosis agents and other dental preparations, coronary agents, laxants, lipid depressants, neural therapeutics, gastro-intestinal agents, migraine remedies, mineral preparations, muscle relaxants, narcotics, parathyroid hormones/calcium-metabolic regulators/osteoporosis remedies, neuropathy preparations and other neurotropic agents,

neurotransmitters (*e.g.*, dopamine) or modified neurotransmitters, ophthalmics, otologics, Parkinson remedies and other remedies against extrapyramidal disturbances, psychopharmacons, sinusitis remedies, roborants/tonics, thyroid therapeutics, serums, immunoglobulins and vaccines, sexual hormones and inhibitors, spasmolytics, platelet aggregation inhibitors, tuberculosis remedies, alterants, urologic agents, vein therapeutics, vitamins, wound treatment agents, cytostatics and metastasis inhibitors.

REMARKS

The purpose of this amendment is to place the claims in better form under United States Patent practice.

The foregoing amendments do not introduce new matter into the present Application, and, therefore should be entered without objection. Support is provided for them as follows:

(a) Support for claim 78 is provided in the English language translation of the specification at the paragraph bridging pages 3-4.

(b) Support for claim 79 is provided by claim 50.

(c) Support for claims 80-112 is provided by claims 1-27 and the English language translation of the specification at the paragraph bridging pages 3-4.

Respectfully submitted,

DANN DORFMAN HERRELL AND SKILLMAN
A Professional Corporation

John S. Child, Jr.

John S. Child, Jr.
PTO Registration No. 28,833
Attorney for Applicant

Attachments: Exhibit A: Claims as amended on April 24, 2001
JSC/gp
G:\SHARED\Georgia\VonKreisler\VonKreis.015\Pleadings\Preliminary Amendment

CLAIMS:

1. Use of colloid-osmotically effective macromolecules for preparing an injectable aqueous solution of at least one pharmaceutically active ingredient for its painless introduction into vessels of the human or animal body.

2. Use of colloid-osmotically effective macromolecules for preparing an injectable aqueous solution of at least one pharmaceutically active ingredient for its tissue-saving introduction into vessels of the human or animal body.

3. Use of colloid-osmotically effective macromolecules for preparing an injectable aqueous solution of at least one pharmaceutically active ingredient for reducing the diffusion of said pharmaceutically active ingredient through the walls of injection vessels of the human or animal body.

4. The use according to any of claims 1 to 3, characterized in that said macromolecule is selected from the group consisting of polysaccharides, modified polysaccharides, peptides and modified peptides, and albumins.

5. The use according to claim 4, characterized in that said polysaccharide is selected from the group consisting of cellulose, starch and dextrane.

6. The use according to claim 4, characterized in that said modified polysaccharide is hydroxyethylstarch [poly(O-hydroxyethyl)starch].

7. The use according to claim 6, characterized in that said hydroxyethylstarch has a degree of substitution, DS, of < 0.4.

8. The use according to claim 6, characterized in that said hydroxyethylstarch has an average molecular weight of below 300,000.

EXHIBIT A

Claims 1-77 as amended on April 24, 2001

9. The use according to claim 6, characterized in that said hydroxyethylstarch has an average molecular weight of below 70,000.

10. The use according to claim 6, characterized in that said hydroxyethylstarch has a degree of substitution, DS, of < 0.4 and an average molecular weight of below 300,000.

11. The use according to claim 5, characterized in that the dextrane has an average molecular weight of below 40,000.

12. The use according to claim 5, characterized in that the dextrane has an average molecular weight of below 15,000.

13. The use according to claim 4, characterized in that gelatin is employed as polypeptide.

14. The use according to claim 4, characterized in that oxypolygelatin or gelatin succinate is employed as modified polypeptide.

15. The use according to claim 14, characterized in that said oxypolygelatin and gelatin succinate have an average molecular weight of below 40,000.

16. The use according to claim 14, characterized in that said oxypolygelatin and gelatin succinate have an average molecular weight of below 15,000.

17. The use according to claim 13, characterized in that said albumins are selected from the group consisting of human albumin, cleavage products of albumin, and recombinant human serum albumin.

18. The use according to any of claims 1, 2 or 3, characterized in that said colloid-forming macromolecules have a colloid-osmotic pressure in aqueous solution of > 1333 Pa (10 mm Hg).

19. The use according to any of claims 1, 2 or 3, characterized in that said colloid-forming macromolecules have a colloid-osmotic pressure in aqueous solution of > 3733 Pa (28 mm Hg).

20. The use according to any of claims 1, 2 or 3, characterized in that the proportion of the colloid-forming macromolecules is from 2 to 25% by weight, based on the total amount of the injectable aqueous solution.

21. The use according to any of claims 1, 2 or 3, characterized in that the proportion of the colloid-forming macromolecules is from 3 to 15% by weight, based on the total amount of the injectable aqueous solution.

22. The use according to any of the preceding claims, characterized in that said injectable aqueous solution additionally has a cation proportion of from 100 to 170 mmol/l and an anion proportion of from 100 to 170 mmol/l.

23. The use according to any of the preceding claims, characterized in that said injectable aqueous solution additionally has a cation proportion of from 100 to 150 mmol/l and an anion proportion of from 100 to 150 mmol/l.

24. The use according to claim 22 or 23, characterized in that part of the cation and/or anion concentration is replaced by a sugar or a natural or synthetic polyol.

25. The use according to claim 1, 2 or 3, characterized in that said injectable aqueous solution has an osmolarity of between 250 and 400 mOsmol/l.

26. The use according to claim 1, characterized in that said pharmaceutically active ingredient is contained in a proportion of from 0.5 to 25% by weight, based on the total amount of the injectable aqueous solution.

27. The use according to claim 1, characterized in that said pharmaceutically active ingredient is selected from the group consisting of slimming preparations/anorexiants, acidose therapeutics, amino acids (e.g., histidine) or

modified amino acids, analeptics/antihypoxemics, analgetics/antirheumatics, anthelmintics, antiallergics, antianemics, antiarrhythmics, antibiotics/antiinfectives, antidementives (nootropics), antidiabetics, antidotes, antiemetics/antivertiginosics, antiepileptics, antihemorrhagics (antifibrinolytics and other hemostatics), antihypertensives, antihypoglycemics, antihypotensives, anticoagulants, antimycotics, antiparasitics (internal), antiphlogistics, antitussives/expectorants, anti-arteriosclerosis agents, balneotherapeutics and agents for heat therapy, beta receptor and calcium channel blockers and inhibitors of the renin-angiotensin system, broncholytics/antiasthmatics, cholagogics and bile duct therapeutics, cholinergics, corticoids (internal), dermatics (internal), dietetics/nutrition therapeutics, diagnostics and agents for diagnostic preliminaries, diuretics, agents stimulating blood flow, withdrawal agents, enzyme inhibitors, enzyme preparations and transport proteins, fibrinolytics, geriatric agents, gout agents, influenza remedies, gynecologic agents, anti-hemorrhoidal agents (proctologics), hepatics, hypnotics/sedatives, hypophysis and hypothalamus hormones, regulatory peptides and their inhibitors, immunotherapeutics and cytokines, infusion and standard injection solutions, organ perfusion solutions, cardiacs, anti-caries and anti-parodontosis agents and other dental preparations, coronary agents, laxants, lipid depressants, neural therapeutics, gastro-intestinal agents, migraine remedies, mineral preparations, muscle relaxants, narcotics, parathyroid hormones/calcium-metabolic regulators/osteoporosis remedies, neuropathy preparations and other neurotropic agents, neurotransmitters (e.g., dopamine) or modified neurotransmitters, ophthalmics, otologics, Parkinson remedies and other remedies against extrapyramidal disturbances, psychopharmacons, sinusitis remedies, roborants/tonics, thyroid therapeutics, serums, immunoglobulins and vaccines, sexual hormones and their inhibitors, spasmolytics, platelet aggregation inhibitors, tuberculosis remedies, alterants, urologic agents, vein therapeutics, vitamins, wound treatment agents, cytostatics and metastasis inhibitors.

28. A kit comprising separately (a) colloid-forming macromolecules in an aqueous solution and (b) a pharmaceutically active ingredient.

29. The kit according to claim 28, characterized in that said pharmaceutically active ingredient is in a solid, liquid or dissolved form.

30. The kit according to claim 28, characterized in that said macromolecule is selected from the group consisting of polysaccharides, modified polysaccharides, polypeptides and modified polypeptides, and albumins.

31. The kit according to claim 30, characterized in that said polysaccharide is selected from the group consisting of cellulose, starch and dextrane.

32. The kit according to claim 30, characterized in that said modified polysaccharide is hydroxyethylstarch [poly(O-hydroxyethyl)starch].

33. The kit according to claim 32, characterized in that said hydroxyethylstarch has a degree of substitution, DS, of < 0.4.

34. The kit according to claim 32, characterized in that said hydroxyethylstarch has an average molecular weight of below 300,000.

35. The kit according to claim 32, characterized in that said hydroxyethylstarch has an average molecular weight of below 70,000.

36. The kit according to claim 32, characterized in that said hydroxyethylstarch has a degree of substitution, DS, of < 0.4 and an average molecular weight of below 300,000.

37. The kit according to claim 31, characterized in that the dextrane has an average molecular weight of below 40,000.

38. The kit according to claim 31, characterized in that the dextrane has an average molecular weight of below 15,000.

39. The kit according to claim 30, characterized in that gelatin is employed as said polypeptide.

40. The kit according to claim 30, characterized in that oxypolygelatin or gelatin succinate is employed as said modified polypeptide.

41. The kit according to claim 40, characterized in that said oxypolygelatin and gelatin succinate have an average molecular weight of below 40,000.

42. The kit according to claim 40, characterized in that said oxypolygelatin and gelatin succinate have an average molecular weight of below 15,000.

43. The kit according to claim 40, characterized in that said albumins are selected from the group consisting of human albumin, cleavage products of albumin, and recombinant human serum albumin.

44. The kit according to claim 28, characterized in that said colloid-forming macromolecules have a colloid-osmotic pressure in aqueous solution of $>$ 1333 Pa (10 mm Hg).

45. The kit according to claim 28, characterized in that said colloid-forming macromolecules have a colloid-osmotic pressure in aqueous solution of $>$ 3733 Pa (28 mm Hg).

46. The kit according to claim 28, characterized in that the proportion of the colloid-forming macromolecules is from 2 to 25% by weight, based on the total amount of the injectable aqueous solution.

47. The kit according to claim 28, characterized in that the proportion of the colloid-forming macromolecules is from 3 to 15% by weight, based on the total amount of the injectable aqueous solution.

48. The kit according to claim 28, characterized in that said injectable aqueous solution additionally has a cation proportion of from 100 to 170 mmol/l and an anion proportion of from 100 to 170 mmol/l.

49. The kit according to claim 28, characterized in that said injectable aqueous solution additionally has a cation proportion of from 100 to 150 mmol/l and an anion proportion of from 100 to 150 mmol/l.

50. The kit according to any of claims 48 or 49, characterized in that part of the cation and/or anion concentration is replaced by a natural or synthetic polyol.

51. The kit according to claim 28, characterized in that said injectable aqueous solution has an osmolarity of between 250 and 400 mOsmol/l.

52. The kit according to claim 28, characterized in that said pharmaceutically active ingredient is selected from the group consisting of slimming preparations/anorexiants, acidose therapeutics, amino acids (e.g., histidine) or modified amino acids, analeptics/antihypoxemics, analgetics/antirheumatics, anthelmintics, antiallergics, antianemics, antiarrhythmics, antibiotics/anti-infectives, antidementives (nootropics), antidiabetics, antidotes, antiemetics/antivertiginosics, antiepileptics, antihemorrhagics (antifibrinolytics and other hemostatics), antihypertensives, antihypoglycemics, antihypotensives, anticoagulants, antimycotics, antiparasitics (internal), antiphlogistics, anti-tussives/expectorants, anti-arteriosclerosis agents, balneotherapeutics and agents for heat therapy, beta receptor and calcium channel blockers and inhibitors of the renin-angiotensin system, broncholytics/antiasthmatics, cholagogics and bile duct therapeutics, cholinergics, corticoids (internal), dermatics (internal), dietetics/nutrition therapeutics, diagnostics and agents for diagnostic preliminaries, diuretics, agents stimulating blood flow, withdrawal agents, enzyme inhibitors, enzyme preparations and transport proteins, fibrinolytics, geriatric agents, gout agents, influenza remedies, gynecologic agents, anti-hemorrhoidal agents (proctologics), hepatics, hypnotics/sedatives, hypophysis and hypothalamus hormones, regulatory peptides and their inhibitors, immunotherapeutics and cytokines, infusion and standard injection solutions, organ perfusion solutions, cardiacs, anti-caries and anti-parodontosis agents and other dental preparations, coronary agents, laxants, lipid depressants, neural therapeutics, gastro-intestinal agents, mi-

graine remedies, mineral preparations, muscle relaxants, narcotics, parathyroid hormones/calcium-metabolic regulators/osteoporosis remedies, neuropathy preparations and other neurotropic agents, neurotransmitters (e.g., dopamine) or modified neurotransmitters, ophthalmics, otologics, Parkinson remedies and other remedies against extrapyramidal disturbances, psychopharmacons, sinusitis remedies, roborants/tonics, thyroid therapeutics, serums, immunoglobulins and vaccines, sexual hormones and their inhibitors, spasmolytics, platelet aggregation inhibitors, tuberculosis remedies, alterants, urologic agents, vein therapeutics, vitamins, wound treatment agents, cytostatics and metastasis inhibitors.

53. The kit according to any of the preceding claims, characterized by additionally containing a perfusor and/or infusion machine.

54. An injectable aqueous medicinal solution comprising at least one pharmaceutically active ingredient and colloid-forming macromolecules selected from the group consisting of polysaccharides or modified polysaccharides, polypeptides, modified polypeptides and albumins, characterized in that said pharmaceutically active ingredients are selected from the group consisting of slimming preparations/anorexiants, acidose therapeutics, amino acids (e.g., histidine) or modified amino acids, analeptics/antihypoxemics, analgetics/antirheumatics, anthelmintics, antiallergics, antianemics, antiarrhythmics, antibiotics/antiinfectives, antidementives (nootropics), antidiabetics, antidotes, antiemetics/antivertiginosics, antiepileptics, antihemorrhagics (antifibrinolytics and other hemostatics), antihypertensives, antihypoglycemics, antihypotensives, anticoagulants, antimycotics, antiparasitics (internal), antiphlogistics, antitussives/expectorants, anti-arteriosclerosis agents, balneotherapeutics and agents for heat therapy, beta receptor and calcium channel blockers and inhibitors of the renin-angiotensin system, broncholytics/antiasthmatics, cholagogics and bile duct therapeutics, cholinergics, corticoids (internal), dermatics (internal), dietetics/nutrition therapeutics, diagnostics and agents for diagnostic preliminaries, diuretics, agents stimulating blood flow, withdrawal agents, enzyme inhibitors, enzyme preparations and transport proteins, fibrinolytics, geriatric agents,

gout agents, influenza remedies, gynecologic agents, anti-hemorrhoidal agents (proctologics), hepatics, hypnotics/sedatives, hypophysis and hypothalamus hormones, regulatory peptides and their inhibitors, immunotherapeutics and cytokines, infusion and standard injection solutions, organ perfusion solutions, cardiacs, anti-caries and anti-parodontosis agents and other dental preparations, coronary agents, laxants, lipid depressants, neural therapeutics, gastro-intestinal agents, migraine remedies, mineral preparations, muscle relaxants, narcotics, parathyroid hormones/calcium-metabolic regulators/osteoporosis remedies, neuropathy preparations and other neurotropic agents, neurotransmitters (e.g., dopamine) or modified neurotransmitters, ophthalmics, otologics, Parkinson remedies and other remedies against extrapyramidal disturbances, psychopharmacons, sinusitis remedies, roborants/tonics, thyroid therapeutics, serums, immunoglobulins and vaccines, sexual hormones and their inhibitors, spasmolytics, platelet aggregation inhibitors, tuberculosis remedies, alterants, urologic agents, vein therapeutics, vitamins, wound treatment agents, cytostatics and metastasis inhibitors.

55. The injectable aqueous medicinal solution according to claim 54, characterized in that said polysaccharide is selected from the group consisting of cellulose, starch and dextrane.

56. The injectable aqueous medicinal solution according to claim 54, characterized in that said modified polysaccharide is hydroxyethylstarch [poly(O-hydroxyethyl)starch].

57. The injectable aqueous medicinal solution according to claim 54, characterized in that said hydroxyethylstarch has a degree of substitution, DS, of < 0.4.

58. The injectable aqueous medicinal solution according to claim 54, characterized in that said hydroxyethylstarch has an average molecular weight of below 300,000.

59. The injectable aqueous medicinal solution according to claim 54, characterized in that said hydroxyethylstarch has an average molecular weight of below 70,000.

60. The injectable aqueous medicinal solution according to claim 54, characterized in that said hydroxyethylstarch has a degree of substitution, DS, of < 0.4 and an average molecular weight of below 300,000.

61. The injectable aqueous medicinal solution according to claim 54, characterized in that the dextrane has an average molecular weight of below 40,000.

62. The injectable aqueous medicinal solution according to claim 54, characterized in that the dextrane has an average molecular weight of below 15,000.

63. The injectable aqueous medicinal solution according to claim 54, characterized in that gelatin is employed as said polypeptide.

64. The injectable aqueous medicinal solution according to claim 54, characterized in that oxypolygelatin or gelatin succinate is employed as said modified polypeptide.

65. The injectable aqueous medicinal solution according to claim 64, characterized in that said oxypolygelatin and gelatin succinate have an average molecular weight of below 40,000.

66. The injectable aqueous medicinal solution according to claim 64, characterized in that said oxypolygelatin and gelatin succinate have an average molecular weight of below 15,000.

67. The injectable aqueous medicinal solution according to claim 63, characterized in that said albumins are selected from the group consisting of human albumin, cleavage products of albumin, and recombinant human serum albumin.

68. The injectable aqueous medicinal solution according to claim 54, characterized in that said colloid-forming macromolecules have a colloid-osmotic pressure in aqueous solution of > 1333 Pa (10 mm Hg).

69. The injectable aqueous medicinal solution according to claim 54, characterized in that said colloid-forming macromolecules have a colloid-osmotic pressure in aqueous solution of > 3733 Pa (28 mm Hg).

70. The injectable aqueous medicinal solution according to claim 55, characterized in that the proportion of the colloid-forming macromolecules is from 2 to 25% by weight, based on the total amount of the injectable aqueous solution.

71. The injectable aqueous medicinal solution according to claim 54, characterized in that the proportion of the colloid-forming macromolecules is from 3 to 15% by weight, based on the total amount of the injectable aqueous solution.

72. The injectable aqueous medicinal solution according to claim 54, characterized in that said injectable aqueous solution additionally has a cation proportion of from 100 to 170 mmol/l and an anion proportion of from 100 to 170 mmol/l.

73. The injectable aqueous medicinal solution according to claim 54, characterized in that said injectable aqueous solution additionally has a cation proportion of from 100 to 150 mmol/l and an anion proportion of from 100 to 150 mmol/l.

74. The injectable aqueous medicinal solution according to claim 54, characterized in that part of the cation and/or anion concentration is replaced by a natural or synthetic polyol.

75. The injectable aqueous medicinal solution according to claim 54, characterized in that said injectable aqueous solution has an osmolarity of between 250 and 400 mOsmol/l.

76. The injectable aqueous medicinal solution according to claim 54, characterized in that said pharmaceutically active ingredient is contained in a proportion of from 0.5 to 25% by weight, based on the total amount of the injectable aqueous solution.

77. An injectable ready medicament comprising the injectable aqueous medicinal solution according to any of claims 54 to 76.

SMB

Painless and Tissue-Saving Injection of Medicaments

The present invention relates to the use of colloid-osmotically effective substances in the infusion or injection of medicaments into vessels of the human or animal body, a kit comprising the individual components, and injectable medicinal solutions.

The injection of medicaments into blood vessels of the body is a frequently used route of administration for medicinal substances. As a rule, a certain amount of the medicinal substance in an aqueous solution or as an emulsion is injected into a small vein extending under the skin. However, with many medicinal substances, tissue damage and/or pain occur immediately after the injection in the area of the vessel into which the medicinal substance has been injected. A first possible cause thereof is the higher concentration of the damaging medicinal substances in the area of the injection site. In addition, the injection of the medicinal substances is often effected with a high hydrostatic pressure. The damage is caused by a contact of the tissue of the vascular wall and of the surrounding connective tissue with the medicinal substances, which are damaging in a higher concentration. Very frequently, medicinal substances in aqueous solutions are adjusted to non-physiological pH values for reasons of stability. After the injection, the tissue of the vascular wall and the surrounding connective tissue are damaged by diffusing protons or hydroxide ions (depending on the titration acidity of the adjusted buffer solutions). Thus, for example, it is known that the inadvertent intra-arterial injection of the narcotic thiopental may lead to massive necroses in the course of the arterial vessel up to loss of the extremity.

According to the prior art, this damage is counteracted by various methods and means. Most frequently, it is attempted to prevent damage by diluting the injected

medicinal substances, either by introducing them into a current infusion, or by mixing with an infusion solution prior to infusion. It is a common feature of all dilution methods that a relatively small quantity of the medicinal substance is mixed with a larger volume of an infusion solution. The drawbacks of these dilution methods reside in the larger volume of liquid which is loaded on the patients, who may suffer from a circulatory disturbance, for example, and in the resulting time for application which is too long for many pharmaceutically active substances. Frequently, a bolus is desired, i.e., injection of a small volume with concentrated medicinal substance within a short period of time, i.e., within a few minutes or seconds.

By infusion into vascular catheters lying in larger vessels (e.g., central vein catheters), potentially damaging medicinal substances can be diluted by the patient's blood after injection. A precondition thereof is the installation of a central vein catheter with all accompanying risks (false puncture, bacterial colonization of the catheter and complicating bacteriaemia) and costs. Another method consists in infusing medicinal substances, not in aqueous solutions, but as an emulsion with fats. However, in this case too, damage and pain occur after the injection of the medicinal substances due to passage of the medicinal substances into the vascular wall and the connective tissue.

To date, colloid-osmotically effective macromolecules, such as hydroxyethylstarch, dextranes and other polysaccharides or polypeptides, such as polygelatin or albumin, have been employed as components of blood and plasma substitute solutions (volume substitutes, plasma expanders). In this case, they serve as a substitute of the colloid-osmotical effect of the endogenous plasma proteins and are therefore infused in hemodynamically relevant amounts, i.e., several grams per day. The infusion volume of such hemodynamically effective solutions is within a range of several hundred milliliters.

Thus, US-A-5,434,191 describes an artificial blood in the form of an aqueous emulsion comprising water, an emulsifier, a synthetic phospholipid, a perfluorinated compound as an oxygen carrier, and a compound selected from the group consisting of hydroxyethylstarch, polyvinylpyrrolidone, modified gelatin, dextrane

or some similar substance which provides for a colloid-osmotic pressure. However, due to the renal complications associated with artificial blood, this system has not yet become established as a blood substitute.

EP-A-0 650 736 describes the use of recombinant human serum albumin (rHSA) for increasing the blood plasma quantity, for supplementing the circulating blood volume, for improving hypoproteinemia, and for maintaining the colloid-osmotic pressure.

As with electrolyte solutions, e.g., physiological salines, some colloidal plasma substitute solutions may also be used as a carrier solution for medicaments. Thus, a medicament is injected into the infusion solution during the infusion and thus diluted in some hundred milliliters of the solution (Rote Liste 1997, Editio Cantor Verlag, No. 52275, Haemaccel). In principle, infusion of such substances causes a permanent increase of the colloid-osmotic pressure in the blood. In order to ensure this effect for a sufficient long period of time, all hemodynamically effective plasma substitutes have a half-life within a range of up to a few hours. All these colloid-osmotically effective macromolecules which exhibit prolonged dwelling times in the blood are first taken up by cells of the reticuloendothelial system and stored depending on the kind of substance.

In a particular application, colloids are used for expanding the interstitial space. Thus, US-A-5,424,288 describes a method for the treatment of tumor cancer in organisms by administering a suspension of macro-aggregated albumin in an inert fluid into the tumor, followed by the injection of a colloidal radioactive agent.

In the Journal of Biological Response Modifiers (1985), 4/4 (340-352), V. Bocci describes a method for increasing the interstitial connective tissue space for subcutaneously or intramuscularly administered medicinal substances, which then arrive in the lymph tracts.

It has been the object of the invention to enable medicaments to be administered into vessels of the human or animal body by appropriate measures in such a way that vascular damage, especially local vascular damage, of the perivascular

connective tissue is highly reduced and, in the ideal case, completely suppressed, and/or that the pain associated with the administration occurs only in a reduced form and, in the ideal case, is completely suppressed. Thus, by appropriate measures, these side-effects on the injection vessel which depend on the concentration of the medicinal substance are to be counteracted. "Injection vessel" as used herein means the vessel (vein, artery etc.) into which the medicinal composition is administered and which communicates with other vessels. Further, it has been the object of the present invention to provide an injectable aqueous medicinal solution (medicament), especially as a ready medicament or as a kit.

The object of the invention was achieved by the use of colloid-osmotically effective substances for preparing an injectable aqueous solution of at least one pharmaceutically active ingredient for its painless and/or tissue-saving introduction into vessels of the human or animal body.

Often, the vascular damage is associated with pain-causing irritations of the perivascular connective tissue so that vascular damage, especially local vascular damage, and pain-causing irritations of the perivascular connective tissue can be reduced and, in the ideal case, completely avoided according to the invention.

The principle according to the invention prevents vasculitis, i.e., an inflammatory response which starts from the wall of the vessels, especially the blood vessels, of the human or animal body.

According to the invention, the diffusion of the pharmaceutically active component through the vascular walls of the injection vessel and the accompanying local vascular damage as well as the pain-causing irritations of the perivascular connective tissue, which may additionally occur, are clearly reduced, preferably completely prevented.

According to the invention, the colloid-osmotically effective substances are natural or synthetic colloid-forming macromolecules which have a colloid-osmotic pressure in aqueous solution of > 1333 Pa (10 mm Hg), preferably > 3733 Pa (28 mm Hg, corresponding to the colloid-osmotic pressure of plasma).

The colloid-forming macromolecules are selected from the group consisting of polysaccharides, modified polysaccharides, polypeptides, modified polypeptides, and proteins, such as albumins.

The polysaccharides are preferably cellulose, starch or dextrane, hydroxyethylstarch [poly(O-hydroxyethyl)starch] being preferred as a polysaccharide. According to the invention, those hydroxyethylstarches may be used, in particular, which have a degree of substitution, DS, of < 0.4. The degree of substitution, DS, is defined as the proportion of substituted anhydroglucose units among all anhydroglucose units. It can be determined from the measured amount of unsubstituted glucose after hydrolysis of a sample. Preferably, the degree of substitution, DS, is at least 0.10, more preferably at least 0.15.

The hydroxyethylstarches employed according to the invention preferably have an average molecular weight of below 300,000, preferably of below 70,000, and even more preferably of below 40,000. More preferably, the hydroxyethylstarch has a degree of substitution, DS, of between 0.1 and < 0.4 and an average molecular weight of below 300,000.

Another polysaccharide which can be employed as a colloid-osmotically effective substance according to the invention is dextrane, preferably having an average molecular weight of below 40,000, more preferably of below 20,000, and even more preferably of below 15,000.

The polypeptides and modified polypeptides employed as colloid-osmotically effective macromolecules according to the invention are selected from the group consisting of gelatin, oxypolygelatin, gelatin succinate. The oxypolygelatin and the gelatin succinate preferably have an average molecular weight of below 40,000, preferably of below 20,000. The proteins are preferably albumin, human albumin, cleavage products of albumin, or recombinant human serum albumin (rHSA).

In contrast to colloids employed as plasma expanders, a sustained effect on the colloid-osmotic pressure in the blood or a prolonged dwelling in the blood as an additional pharmacological effect is not desired according to the invention. For the

effect intended according to the invention, it is only necessary for the colloids to remain within the vascular system of the injection vessel and to have a transient colloid-osmotic effect. Ideally, the substances are excreted from the body already during the first passage through the kidneys. It is known that the serum half-life of the hydroxyethylstarch primarily depends on its degree of substitution, DS. Its molecular weight plays a rather inferior role. However, for the water-solubility of the starch, a minimum amount of hydroxyethyl groups is necessary. A low-substitution hydroxyethylstarch having a degree of substitution of below 0.4, for example, having an average degree of substitution of 0.3, would have a satisfactory colloid-osmotic effect in the infusion vessel for sufficiently high molecular weights, but would be excreted (e.g., renally eliminated) from the body very quickly after the infusion. Due to its quick elimination, this hydroxyethylstarch would be hardly useful as a plasma expander. A relevant load on the reticuloendothelial system or a cumulative storage in organs would not occur even upon repeated injections.

For the other colloidal plasma expanders mentioned above, there is a pharmacokinetic relationship between the molecular weight and the serum half-life. Accordingly, for dextranes having an average molecular weight of below 40,000, preferably below 20,000, a correspondingly quicker elimination from the body can be observed. Also with oxypolygelatin or gelatin succinate, a quick elimination from the body can be caused by an average molecular weight of below 40,000, preferably below 20,000, more preferably below 15,000. A substantial increase of the colloid-osmotic pressure in the patient's blood cannot be induced permanently even by quantitatively larger infusions of such solutions having lower average molecular weights.

Independently of pharmacokinetics, the application of a colloid-osmotically effective principle means an injection of low quantities of colloidal macromolecules. A volume of 10 ml of a claimed injection solution having a colloid concentration of 10% contains 1 g of colloid, whereas the injection of medicaments into colloidal plasma substitute solutions (plasma expanders) as carrier solutions causes a colloid load of 50 g, a significant increase of the colloid-osmotic pressure in the

patient's blood, and a frequently undesirable dilution or too slow an administration of the medicinal substance.

The proportion of the colloid-osmotically effective substance is from 2 to 25% by weight, preferably from 3 to 15% by weight, based on the total amount of the injectable aqueous solution.

The injectable aqueous solutions of medicinal substances employed according to the invention have an osmolarity of between 250 and 400 mOsmol/l, preferably between 300 and 350 mOsmol/l. The tonicity of the solution to be injected can be adjusted by an additional cation proportion of from 100 to 170 mmol/l, preferably from 100 to 150 mmol/l, and an anion proportion of from 100 to 170 mmol/l, preferably from 100 to 150 mmol/l. Part of the cation and/or anion concentration can be replaced by a natural or synthetic polyol. Polyols suitable for this purpose are known in the prior art. In an illustrative way, there may be mentioned sugars, such as glucose, and synthetic polyols, such as sorbitol or xylitol.

The pH value of the solution employed is essentially determined by the requirements in terms of the stability in aqueous solution of the medicinal substance to be administered. The pH value may be between 1.5 and 12, preferably between 4.5 and 8. The solutions used according to the invention are free of particles and free of emulsion-forming perfluorinated organic compounds. Thus, the compositions used according to the invention are neither emulsions nor suspensions. The injectable compositions may further contain additives and auxiliaries which are common in infusion therapy and physiologically acceptable, such as buffer systems. As a buffer, the amino acid histidine, preferably in a dosage of from 50 to 150 mmol/l, and histidine hydrochloride, preferably in a dosage of from 5 to 20 mmol/l, may be added to the solution.

According to the invention, medicinal substances can be employed as the pharmaceutically active ingredient which are selected from the group consisting of slimming preparations/anorexiants, acidose therapeutics, amino acids (e.g., histidine) or modified amino acids, analeptics/antihypoxemics, analgetics/antirheumatics, anthelmintics, antiallergics, antianemics, antiarrhythmics, antibiotics/

antiinfectives, antidementives (nootropics), antidiabetics, antidotes, antiemetics/ antivertiginosics, antiepileptics, antihemorrhagics (antifibrinolytics and other hemostatics), antihypertensives, antihypoglycemics, antihypotensives, anticoagulants, antimycotics, antiparasitics (internal), antiphlogistics, antitussives/expectorants, anti-arteriosclerosis agents, balneotherapeutics and agents for heat therapy, beta receptor and calcium channel blockers and inhibitors of the renin-angiotensin system, broncholytics/antiasthmatics, cholagogics and bile duct therapeutics, cholinergics, corticoids (internal), dermatics (internal), dietetics/ nutrition therapeutics, diagnostics and agents for diagnostic preliminaries, diuretics, agents stimulating blood flow, withdrawal agents, enzyme inhibitors, enzyme preparations and transport proteins, fibrinolytics, geriatric agents, gout agents, influenza remedies, gynecologic agents, anti-hemorrhoidal agents (proctologics), hepatics, hypnotics/sedatives, hypophysis and hypothalamus hormones, regulatory peptides and their inhibitors, immunotherapeutics and cytokines, infusion and standard injection solutions, organ perfusion solutions, cardiacs, anti-caries and anti-parodontosis agents and other dental preparations, coronary agents, laxants, lipid depressants, neural therapeutics, gastro-intestinal agents, migraine remedies, mineral preparations, muscle relaxants, narcotics, parathyroid hormones/calcium-metabolic regulators/osteoporosis remedies, neuropathy preparations and other neurotropic agents, neurotransmitters (e.g., dopamine) or modified neurotransmitters, ophthalmics, otologics, Parkinson remedies and other remedies against extrapyramidal disturbances, psychopharmacons, sinusitis remedies, roborants/ tonics, thyroid therapeutics, serums, immunoglobulins and vaccines, sexual hormones and their inhibitors, spasmolytics, platelet aggregation inhibitors, tuberculosis remedies, alterants, urologic agents, vein therapeutics, vitamins, wound treatment agents, cytostatics and metastasis inhibitors. The pharmaceutically active ingredient may be contained in the injectable solution in a proportion of from 0.5 to 25% by weight, preferably from 2 to 15% by weight, more preferably from 5 to 10% by weight, based on the total amount of the injectable solution.

The aqueous medicinal solutions used according to the invention can be favorably affected by the colloids employed in terms of water-solubility, stability, rheological properties and viscosity. Similarly, advantageous changes in terms of electric conductivity, filtration properties, temperature conductance, acoustic resonance,

chemoluminescence and phagocytability are possible by appropriately selecting the colloid-osmotically effective substance.

The invention further relates to a kit comprising the components of the composition used according to the invention in a separated form. In detail, the kit comprises the colloid-osmotically effective substance in an aqueous solution and, separately, the medicinal substance in a solid, liquid or dissolved form. For the colloid-osmotically effective substance and the pharmaceutically active substances, reference is made to the above statements. Prior to application (injection, infusion), the two components are mixed and administered using a perfusor and/or infusion machine, which may also be independently contained in the kit. The perfusor or the infusion machine may be controlled by a processor which receives signals from a measuring device or input appliance. For the properties and the other components which may be contained in the aqueous injectable solution, reference is made to the above statements.

In another particular embodiment, the invention relates to an injectable aqueous medicinal solution comprising at least one pharmaceutically active ingredient selected from the group described above, and a colloid-osmotically effective substance selected from the group described above, especially from the group consisting of polysaccharides, modified polysaccharides and gelatin. The polysaccharides and modified polysaccharides are selected from the group consisting of starch and modified starch. However, it is particularly preferred to use the hydroxyethylstarch described in more detail above in the way described in detail above.

In the form of their ready medicament, the above described injectable aqueous medicinal solutions are suitable for injecting medicinal substances which, if injected in another form, would lead to tissue damage and/or pain.

The preparation of the injectable aqueous medicinal solution can be effected according to known methods of the prior art, especially by mixing the individual components to form the solution. For preparing the kit, the individual components are filled in suitable containers, sealed and provided separately in the form of the

kit until use. According to the invention, pharmaceutically active substances can be injected quickly and in high concentrations while the vascular damage, especially local vascular damage, at the site of injection is reduced, and usually even completely suppressed. Due to the reduction of the irritations of the perivascular connective tissue, hardly any pain, or none at all, occurs at the site of injection.

Particularly advantageous is the possibility to administer small boluses, especially injection boluses of up to 20 ml, preferably up to 10 ml, more preferably up to 5 ml, or infusion boluses of up to 100 ml, preferably up to 50 ml.

Example

In a 10% by weight aqueous solution of hydroxyethylstarch (DS < 0.4; average molecular weight < 70,000), 20 mg of etomidate was dissolved in the presence of 100 mmol/l of anion proportion and 100 mmol/l of cation proportion, and quickly injected intravenously. The injection proceeded without pain.

CLAIMS:

1. Use of colloid-osmotically effective substances for preparing an injectable aqueous solution of at least one pharmaceutically active ingredient for its painless introduction into vessels of the human or animal body.

2. Use of colloid-osmotically effective substances for preparing an injectable aqueous solution of at least one pharmaceutically active ingredient for its tissue-saving introduction into vessels of the human or animal body.

3. Use of colloid-osmotically effective substances for preparing an injectable aqueous solution of at least one pharmaceutically active ingredient for reducing the diffusion of said pharmaceutically active ingredient through the walls of injection vessels of the human or animal body.

4. The use according to any of claims 1, 2 or 3, characterized in that colloid-forming macromolecules are employed as said colloid-osmotically effective substance.

5. The use according to claim 4, characterized in that said macromolecule is selected from the group consisting of polysaccharides, modified polysaccharides, peptides and modified peptides, and albumins.

6. The use according to claim 5, characterized in that said polysaccharide is selected from the group consisting of cellulose, starch and dextrane.

7. The use according to claim 5, characterized in that said modified polysaccharide is hydroxyethylstarch [poly(O-hydroxyethyl)starch].

8. The use according to claim 7, characterized in that said hydroxyethylstarch has a degree of substitution, DS, of < 0.4.

9. The use according to claim 7, characterized in that said hydroxyethylstarch has an average molecular weight of below 300,000.

10. The use according to claim 7, characterized in that said hydroxyethylstarch has an average molecular weight of below 70,000.

11. The use according to claim 7, characterized in that said hydroxyethylstarch has a degree of substitution, DS, of < 0.4 and an average molecular weight of below 300,000.

12. The use according to claim 6, characterized in that the dextrane has an average molecular weight of below 40,000.

13. The use according to claim 6, characterized in that the dextrane has an average molecular weight of below 15,000.

14. The use according to claim 5, characterized in that gelatin is employed as polypeptide.

15. The use according to claim 5, characterized in that oxypolygelatin or gelatin succinate is employed as modified polypeptide.

16. The use according to claim 5, characterized in that said oxypolygelatin and gelatin succinate have an average molecular weight of below 40,000.

17. The use according to claim 15, characterized in that said oxypolygelatin and gelatin succinate have an average molecular weight of below 15,000.

18. The use according to claim 14, characterized in that said albumins are selected from the group consisting of human albumin, cleavage products of albumin, and recombinant human serum albumin.

19. The use according to any of claims 1, 2 or 3, characterized in that said colloid-osmotically effective substance has a colloid-osmotic pressure in aqueous solution of > 1333 Pa (10 mm Hg).

20. The use according to any of claims 1, 2 or 3, characterized in that said colloid-osmotic substance has a colloid-osmotic pressure in aqueous solution of > 3733 Pa (28 mm Hg).

21. The use according to any of claims 1, 2 or 3, characterized in that the proportion of the colloid-osmotically effective substance is from 2 to 25% by weight, based on the total amount of the injectable aqueous solution.

22. The use according to any of claims 1, 2 or 3, characterized in that the proportion of the colloid-osmotically effective substance is from 3 to 15% by weight, based on the total amount of the injectable aqueous solution.

23. The use according to any of the preceding claims, characterized in that said injectable aqueous solution additionally has a cation proportion of from 100 to 170 mmol/l and an anion proportion of from 100 to 170 mmol/l.

24. The use according to any of the preceding claims, characterized in that said injectable aqueous solution additionally has a cation proportion of from 100 to 150 mmol/l and an anion proportion of from 100 to 150 mmol/l.

25. The use according to claim 23 or 24, characterized in that part of the cation and/or anion concentration is replaced by a sugar or a natural or synthetic polyol.

26. The use according to claim 1, 2 or 3, characterized in that said injectable aqueous solution has an osmolarity of between 250 and 400 mOsmol/l.

27. The use according to claim 1, characterized in that said pharmaceutically active ingredient is contained in a proportion of from 0.5 to 25% by weight, based on the total amount of the injectable aqueous solution.

28. The use according to claim 1, characterized in that said pharmaceutically active ingredient is selected from the group consisting of slimming preparations/anorexiants, acidose therapeutics, amino acids (e.g., histidine) or

modified amino acids, analeptics/antihypoxemics, analgetics/antirheumatics, anthelmintics, antiallergics, antianemics, antiarrhythmics, antibiotics/antiinfectives, antidementives (nootropics), antidiabetics, antidotes, antiemetics/antivertiginosics, antiepileptics, antihemorrhagics (antifibrinolytics and other hemostatics), antihypertensives, antihypoglycemics, antihypotensives, anticoagulants, antimycotics, antiparasitics (internal), antiphlogistics, antitussives/expectorants, anti-arteriosclerosis agents, balneotherapeutics and agents for heat therapy, beta receptor and calcium channel blockers and inhibitors of the renin-angiotensin system, broncholytics/antiasthmatics, cholagogics and bile duct therapeutics, cholinergics, corticoids (internal), dermatics (internal), dietetics/nutrition therapeutics, diagnostics and agents for diagnostic preliminaries, diuretics, agents stimulating blood flow, withdrawal agents, enzyme inhibitors, enzyme preparations and transport proteins, fibrinolytics, geriatric agents, gout agents, influenza remedies, gynecologic agents, anti-hemorrhoidal agents (proctologics), hepatics, hypnotics/sedatives, hypophysis and hypothalamus hormones, regulatory peptides and their inhibitors, immunotherapeutics and cytokines, infusion and standard injection solutions, organ perfusion solutions, cardiacs, anti-caries and anti-parodontosis agents and other dental preparations, coronary agents, laxants, lipid depressants, neural therapeutics, gastro-intestinal agents, migraine remedies, mineral preparations, muscle relaxants, narcotics, parathyroid hormones/calcium-metabolic regulators/osteoporosis remedies, neuropathy preparations and other neurotropic agents, neurotransmitters (e.g., dopamine) or modified neurotransmitters, ophthalmics, otologics, Parkinson remedies and other remedies against extrapyramidal disturbances, psychopharmacons, sinusitis remedies, roborants/tonics, thyroid therapeutics, serums, immunoglobulins and vaccines, sexual hormones and their inhibitors, spasmolytics, platelet aggregation inhibitors, tuberculosis remedies, alterants, urologic agents, vein therapeutics, vitamins, wound treatment agents, cytostatics and metastasis inhibitors.

29. A method for the painless injection of an aqueous solution comprising at least one pharmaceutically active ingredient as defined in claim 28, charac-

terized in that said aqueous injection solution contains a colloid-osmotically effective substance as defined in any of claims 4 to 26.

30. A method for the tissue-saving injection of an aqueous solution comprising at least one pharmaceutically active ingredient as defined in claim 28, characterized in that said aqueous injection solution contains a colloid-osmotically effective substance as defined in any of claims 4 to 26.

31. A kit comprising separately (a) a colloid-osmotically effective substance in an aqueous solution and (b) a pharmaceutically active ingredient.

32. The kit according to claim 31, characterized in that said pharmaceutically active ingredient is in a solid, liquid or dissolved form.

33. The kit according to claim 31, characterized in that colloid-forming macromolecules are employed as said colloid-osmotically effective substance.

34. The kit according to claim 33, characterized in that said macromolecule is selected from the group consisting of polysaccharides, modified polysaccharides, polypeptides and modified polypeptides, and albumins.

35. The kit according to claim 34, characterized in that said polysaccharide is selected from the group consisting of cellulose, starch and dextrane.

36. The kit according to claim 34, characterized in that said modified polysaccharide is hydroxyethylstarch [poly(O-hydroxyethyl)starch].

37. The kit according to claim 36, characterized in that said hydroxyethylstarch has a degree of substitution, DS, of < 0.4.

38. The kit according to claim 36, characterized in that said hydroxyethylstarch has an average molecular weight of below 300,000.

39. The kit according to claim 36, characterized in that said hydroxyethylstarch has an average molecular weight of below 70,000.

40. The kit according to claim 36, characterized in that said hydroxyethylstarch has a degree of substitution, DS, of < 0.4 and an average molecular weight of below 300,000.

41. The kit according to claim 35, characterized in that the dextrane has an average molecular weight of below 40,000.

42. The kit according to claim 35, characterized in that the dextrane has an average molecular weight of below 15,000.

43. The kit according to claim 34, characterized in that gelatin is employed as said polypeptide.

44. The kit according to claim 34, characterized in that oxypolygelatin or gelatin succinate is employed as said modified polypeptide.

45. The kit according to claim 44, characterized in that said oxypolygelatin and gelatin succinate have an average molecular weight of below 40,000.

46. The kit according to claim 44, characterized in that said oxypolygelatin and gelatin succinate have an average molecular weight of below 15,000.

47. The kit according to claim 43, characterized in that said albumins are selected from the group consisting of human albumin, cleavage products of albumin, and recombinant human serum albumin.

48. The kit according to claim 31, characterized in that said colloid-osmotically effective substance has a colloid-osmotic pressure in aqueous solution of > 1333 Pa (10 mm Hg).

49. The kit according to claim 31, characterized in that said colloid-osmotic substance has a colloid-osmotic pressure in aqueous solution of > 3733 Pa (28 mm Hg).

50. The kit according to claim 31, characterized in that the proportion of the colloid-osmotically effective substance is from 2 to 25% by weight, based on the total amount of the injectable aqueous solution.

51. The kit according to claim 31, characterized in that the proportion of the colloid-osmotically effective substance is from 3 to 15% by weight, based on the total amount of the injectable aqueous solution.

52. The kit according to claim 31, characterized in that said injectable aqueous solution additionally has a cation proportion of from 100 to 170 mmol/l and an anion proportion of from 100 to 170 mmol/l.

53. The kit according to claim 31, characterized in that said injectable aqueous solution additionally has a cation proportion of from 100 to 150 mmol/l and an anion proportion of from 100 to 150 mmol/l.

54. The kit according to any of claims 52 or 53, characterized in that part of the cation and/or anion concentration is replaced by a natural or synthetic polyol.

55. The kit according to claim 31, characterized in that said injectable aqueous solution has an osmolarity of between 250 and 400 mOsmol/l.

56. The kit according to claim 31, characterized in that said pharmaceutically active ingredient is selected from the group consisting of slimming preparations/anorexiants, acidose therapeutics, amino acids (e.g., histidine) or modified amino acids, analeptics/antihypoxemics, analgetics/antirheumatics, anthelmintics, antiallergics, antianemics, antiarrhythmics, antibiotics/anti-infectives, antidementives (nootropics), antidiabetics, antidotes, antiemetics/antivertiginosics, antiepileptics, antihemorrhagics (antifibrinolytics and other hemostatics), antihypertensives, antihypoglycemics, antihypotensives, anticoagulants, antimycotics, antiparasitics (internal), antiphlogistics, antitussives/expectorants, anti-arteriosclerosis agents, balneotherapeutics and agents for heat therapy, beta receptor and calcium channel blockers and in-

hibitors of the renin-angiotensin system, broncholytics/antiasthmatics, cholagogics and bile duct therapeutics, cholinergics, corticoids (internal), dermatics (internal), dietetics/nutrition therapeutics, diagnostics and agents for diagnostic preliminaries, diuretics, agents stimulating blood flow, withdrawal agents, enzyme inhibitors, enzyme preparations and transport proteins, fibrinolytics, geriatric agents, gout agents, influenza remedies, gynecologic agents, anti-hemorrhoidal agents (proctologics), hepatics, hypnotics/sedatives, hypophysis and hypothalamus hormones, regulatory peptides and their inhibitors, immunotherapeutics and cytokines, infusion and standard injection solutions, organ perfusion solutions, cardiacs, anti-caries and anti-parodontosis agents and other dental preparations, coronary agents, laxants, lipid depressants, neural therapeutics, gastro-intestinal agents, migraine remedies, mineral preparations, muscle relaxants, narcotics, parathyroid hormones/calcium-metabolic regulators/osteoporosis remedies, neuropathy preparations and other neurotropic agents, neurotransmitters (e.g., dopamine) or modified neurotransmitters, ophthalmics, otologics, Parkinson remedies and other remedies against extrapyramidal disturbances, psychopharmacons, sinusitis remedies, roborants/tonics, thyroid therapeutics, serums, immunoglobulins and vaccines, sexual hormones and their inhibitors, spasmolytics, platelet aggregation inhibitors, tuberculosis remedies, alterants, urologic agents, vein therapeutics, vitamins, wound treatment agents, cytostatics and metastasis inhibitors.

57. The kit according to any of the preceding claims, characterized by additionally containing a perfusor and/or infusion machine.

58. An injectable aqueous medicinal solution comprising at least one pharmaceutically active ingredient and a colloid-osmotically effective substance selected from the group consisting of polysaccharides or modified polysaccharides, polypeptides, modified polypeptides and albumins.

59. The injectable aqueous medicinal solution according to claim 58, characterized in that said polysaccharide is selected from the group consisting of cellulose, starch and dextrane.

60. The injectable aqueous medicinal solution according to claim 58, characterized in that said modified polysaccharide is hydroxyethylstarch [poly(O-hydroxyethyl)starch].

61. The injectable aqueous medicinal solution according to claim 58, characterized in that said hydroxyethylstarch has a degree of substitution, DS, of < 0.4.

62. The injectable aqueous medicinal solution according to claim 58, characterized in that said hydroxyethylstarch has an average molecular weight of below 300,000.

63. The injectable aqueous medicinal solution according to claim 58, characterized in that said hydroxyethylstarch has an average molecular weight of below 70,000.

64. The injectable aqueous medicinal solution according to claim 58, characterized in that said hydroxyethylstarch has a degree of substitution, DS, of < 0.4 and an average molecular weight of below 300,000.

65. The injectable aqueous medicinal solution according to claim 58, characterized in that the dextrane has an average molecular weight of below 40,000.

66. The injectable aqueous medicinal solution according to claim 58, characterized in that the dextrane has an average molecular weight of below 15,000.

67. The use according to claim 58, characterized in that gelatin is employed as said polypeptide.

68. The use according to claim 58, characterized in that oxypolygelatin or gelatin succinate is employed as said modified polypeptide.

69. The use according to claim 68, characterized in that said oxypolygelatin and gelatin succinate have an average molecular weight of below 40,000.

70. The use according to claim 68, characterized in that said oxypolygelatin and gelatin succinate have an average molecular weight of below 15,000.

71. The use according to claim 67, characterized in that said albumins are selected from the group consisting of human albumin, cleavage products of albumin, and recombinant human serum albumin.

72. The injectable aqueous medicinal solution according to claim 58, characterized in that said colloid-osmotically effective substance has a colloid-osmotic pressure in aqueous solution of > 1333 Pa (10 mm Hg).

73. The injectable aqueous medicinal solution according to claim 58, characterized in that said colloid-osmotic substance has a colloid-osmotic pressure in aqueous solution of > 3733 Pa (28 mm Hg).

74. The injectable aqueous medicinal solution according to claim 59, characterized in that the proportion of the colloid-osmotically effective substance is from 2 to 25% by weight, based on the total amount of the injectable aqueous solution.

75. The injectable aqueous medicinal solution according to claim 58, characterized in that the proportion of the colloid-osmotically effective substance is from 3 to 15% by weight, based on the total amount of the injectable aqueous solution.

76. The injectable aqueous medicinal solution according to claim 58, characterized in that said injectable aqueous solution additionally has a cation proportion of from 100 to 170 mmol/l and an anion proportion of from 100 to 170 mmol/l.

77. The injectable aqueous medicinal solution according to claim 58, characterized in that said injectable aqueous solution additionally has a cation proportion of from 100 to 150 mmol/l and an anion proportion of from 100 to 150 mmol/l.

78. The injectable aqueous medicinal solution according to claim 58, characterized in that part of the cation and/or anion concentration is replaced by a natural or synthetic polyol.

79. The injectable aqueous medicinal solution according to claim 58, characterized in that said injectable aqueous solution has an osmolarity of between 250 and 400 mOsmol/l.

80. The injectable aqueous medicinal solution according to claim 58, characterized in that said pharmaceutically active ingredient is contained in a proportion of from 0.5 to 25% by weight, based on the total amount of the injectable aqueous solution.

81. The injectable aqueous medicinal solution according to claim 58, characterized in that said pharmaceutically active ingredient is selected from the group consisting of slimming preparations/anorexiants, acidose therapeutics, amino acids (e.g., histidine) or modified amino acids, analeptics/antihypoxemics, analgetics/antirheumatics, anthelmintics, antiallergics, antianemics, antiarrhythmics, antibiotics/antiinfectives, antidementives (nootropics), antidiabetics, antidotes, antiemetics/antivertiginosics, antiepileptics, antihemorrhagics (antifibrinolytics and other hemostatics), antihypertensives, antihypoglycemics, antihypotensives, anticoagulants, antimycotics, antiparasitics (internal), antiphlogistics, antitussives/expectorants, antiarteriosclerosis agents, balneotherapeutics and agents for heat therapy, beta receptor and calcium channel blockers and inhibitors of the renin-angiotensin system, broncholytics/antiasthmatics, cholagogics and bile duct therapeutics, cholinergics, corticoids (internal), dermatics (internal), dietetics/nutrition therapeutics, diagnostics and agents for diagnostic preliminaries, diuretics, agents stimulating blood flow, withdrawal agents, enzyme inhibitors, enzyme preparations and transport proteins, fibrinolytics, geriatric agents, gout agents, influenza remedies, gynecologic agents, antihemorrhoidal agents (proctologics), hepatics, hypnotics/sedatives, hypophysis and hypothalamus hormones, regulatory peptides and their inhibitors, immunotherapeutics and cytokines, infusion and standard injection solu-

tions, organ perfusion solutions, cardiacs, anti-caries and anti-parodontosis agents and other dental preparations, coronary agents, laxants, lipid depressants, neural therapeutics, gastro-intestinal agents, migraine remedies, mineral preparations, muscle relaxants, narcotics, parathyroid hormones/calcium-metabolic regulators/osteoporosis remedies, neuropathy preparations and other neurotropic agents, neurotransmitters (e.g., dopamine) or modified neurotransmitters, ophthalmics, otologics, Parkinson remedies and other remedies against extrapyramidal disturbances, psychopharmacons, sinusitis remedies, roborants/tonics, thyroid therapeutics, serums, immunoglobulins and vaccines, sexual hormones and their inhibitors, spasmolytics, platelet aggregation inhibitors, tuberculosis remedies, alterants, urologic agents, vein therapeutics, vitamins, wound treatment agents, cytostatics and metastasis inhibitors.

82. An injectable ready medicament comprising the injectable aqueous medicinal solution according to any of claims 58 to 81.

DECLARATION, POWER OF ATTORNEY AND POWER TO INSPECT

As a below named inventor, I hereby declare:

that my residence, post office address and citizenship are as stated below next to my name;

that I verily believe I am an original, first and joint inventor (if plural inventors are named below) of the Invention entitled: **"PAINLESS AND TISSUE SAVING INJECTION OF MEDICAMENTS"**

the specification of which [check one(s) applicable]:

X was first described and claimed in German Patent Application Serial No. **DE 199 07 257.4** filed on **February 21, 1999**;
X was filed as PCT International/U.S. Application No. **PCT/EP/00/01357** on **February 18, 2000** (International Filing Date)
___ and was amended by Amendments filed _____ (if applicable); [or];
X is attached to this Declaration, Power of Attorney and Power to Inspect;

that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above; and

that I acknowledge my duty to disclose information which is material to the examination of this application in accordance with Rule 56(a) [37CFR§1.56(a)].

POWER OF ATTORNEY: As inventor, I hereby appoint the practitioners associated with **Customer No. 000110** as my attorneys or agents with full power of substitution to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: **John S. Child Jr., Reg. No. 28,833**

POWER TO INSPECT: I hereby give **DANN, DORFMAN, HERRELL AND SKILLMAN, P.C.** of Philadelphia, PA or its duly accredited representatives power to inspect and obtain copies of the papers on file relating to this application.

SEND CORRESPONDENCE TO: CUSTOMER NUMBER 000110

DIRECT INQUIRIES TO: **John S. Child, Jr.** **Telephone: (215) 563-4100** **Facsimile: (215) 563-4044**

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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